Sleeve Lobectomy Compared with Pneumonectomy after Induction Therapy for Non–Small-Cell Lung Cancer

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Background: We compared morbidity, mortality, and oncological results of bronchial and/or vascular sleeve lobectomy (SL) with those of pneumonectomy (PN) after induction therapy for lung cancer.

Methods: Between 1998 and 2011, 82 patients receiving induction therapy (chemo or chemo-radiotherapy) for non–small-cell-lung-cancer underwent sleeve lobectomy ($n = 39$) or pneumonectomy ($n = 43$). Only patients undergoing preoperative chemotherapy (39 in the SL group and 39 in the PN group) were included in the study. SL was bronchial in 21, vascular in 12, and broncho-vascular in six cases, respectively. Clinical stage before induction therapy was IIb in seven patients (1 in PN group; 6 in SL group), IIIa in 66 (36 in PN group; 30 in SL group), and IIIb in five patients (2 in PN group; 3 in SL group), respectively. N3 patients were not included in this series.

Results: The rate of downstaged patients (pathological complete response and stage I–II) was 79.5% in the SL group and 53.8% in the PN group ($p = 0.01$).Postpneumonectomy mortality rate was 2.6 %. There was no postoperative mortality after SL. Complications occurred in 12 patients (30.8%) after PN and in 11 patients (28.2%) after SL ($p = 0.6$). Three-year and 5-year survival rates were 68 ± 3% and 64 ± 8% in the SL group; and 59.5 ± 5% and 34.5 ± 8% in the PN group ($p = 0.02$). The difference in terms of recurrence rate (locoregional and distant) between the two groups was not significant ($p = 0.2$).

Conclusions: SL represents a valid therapeutic option even after induction chemotherapy, providing better long-term survival than PN, with no increase of postoperative complications or recurrence rate. Pathological downstaging is a favorable prognostic factor.

Key Words: Induction therapy, Non–small-cell lung cancer, Pneumonectomy, Sleeve lobectomy.

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Lobectomy associated with resection and reconstruction of the bronchus, the pulmonary artery (PA), or both has proved to be a valid therapeutic option for the treatment of centrally located non–small-cell lung cancer (NSCLC).[1] These are generally accepted operations to avoid pneumonectomy (PN) in patients with compromised cardiac and/or pulmonary function, but recent experiences have shown that the advantages of sparing lung parenchyma are evident also in patients without cardio-pulmonary impairment.[2]

Moreover, there is clear evidence that sleeve lobectomy (SL) is oncologically comparable with PN, with no increased postoperative morbidity, lower mortality, and better quality of life because of functional preserving (Table 1).[3–14] Literature studies in this setting generally refer to patients not undergoing preoperative chemotherapy or chemo-radiotherapy, and very few data, comparing SL with PN after induction therapy, are available.

Although the beneficial effects of neoadjuvant therapy on the prognosis of patients with locally advanced lung cancer have been largely proven, concern about an increased risk of complications, when complex reconstructive procedures are performed after oncological treatment, has limited the diffusion of such operations within multimodality treatment options. Tissue damage and fibrotic alterations induced by induction therapy may compromise the healing of the reconstructed structures, and therefore, are the main technical aspects influencing the intraoperative and postoperative morbidity risk.

In this study, we compare morbidity, mortality, and long-term oncological results of lobectomy associated with broncho-vascular reconstruction with those of PN after chemotherapy. Moreover, postoperative outcome of patients undergoing sleeve lobectomy after induction treatment is compared with that of patients receiving the same operation without preoperative treatment.

PATIENTS AND METHODS

Between 1998 and 2011, 82 patients with NSCLC underwent bronchial and/or vascular SL (39 patients; 47.6%) or PN (43 patients; 52.4%) after induction chemotherapy or chemo-radiotherapy. Only patients undergoing preoperative chemotherapy (39 in the SL group and 39 in the PN group) were included in the study. The four patients receiving induction chemo-radiotherapy in the PN group were excluded because the preoperative irradiation could represent a factor influencing results. Patients undergoing previous surgical exploration were not included. We also excluded N3 cases.

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TABLE 1. Literature Data

Author		Patients (*n*)	Complications (%)	Mortality (%)	L-Recurrence (%)	D-Recurrence (%)	Stage I 5-Year Survival (%)	Stage II 5-Year Survival (%)	Stage III 5-Year Survival (%)	Overall 5-Year Survival (%)
Gaissert et al.[3]	SL	72	11	4	14	—	—	53	—	42
	PN	56	16	9	—	—	—	43	—	44
Okada et al.[4]	SL	60	13	2.8	8	—	—	—	—	48
	PN	60	22	2	10	—	—	—	—	28
Deslauriers et al.[5]	SL	184	—	1.6	22	—	66	50	19	52
	PN	1046	—	5.3	35	—	50	34	22	31
Bagan et al.[7]	SL	66	28.8	4.5	4.5	—	—	—	—	72.5
	PN	151	29.9	12.6	7.6	—	—	—	—	51.2
Kim et al.[8]	SL	49	7.4	6.1	22	22	88	52	8	53.7
	PN	49	44	4.1	6	20	75	36	38	59.5
Lausberg et al.[9]	SL	171	0.6[a]	1.7	36.2	—	—	—	—	45
	PN	63	7.9[a]	6.3	21.3	—	—	—	—	30.4
Ludwig et al.[6]	SL	116	38	4.3	—	—	57	40	22	39
	PN	194	26	4.6	—	—	45	42	13	27
Takeda et al.[10]	SL	62	45	4.8	9.7	29	—	—	—	54.1
	PN	110	40.9	3.6	10.9	49.7	—	—	—	32.9
Parissis et al.[12]	SL	79	16.4	2.5	17.7	—	75	53	16	46.8
	PN	129	21.6	8.5	19.4	—	64	50	18	37.1
Park et al.[13]	SL	105	29.5	1	14.3	11.4	—	—	—	58.4
	PN	105	33.4	8.6	16.2	21.9	—	—	—	32.1
Gomez-Caro et al.[23]	SL	55	32	3.6	3.6	38	—	—	—	61
	PN	21	33	5	33	71	—	—	—	31

Results of studies comparing SL with PN: complications, mortality, recurrence rate, survival.
[a] Bronchial complications.
D-recurrence, distant recurrence; L-recurrence, locoregional recurrence; SL, sleeve lobectomy; PN, pneumonectomy.

There was no complete correspondence in the distribution of the two surgical procedures over time: PN had a prevalent distribution in the first part of the study period, whereas SL had a prevalent distribution in the second part of the study period.

Demographic data and clinical stages before induction chemotherapy regimen of the 78 patients included in the study are reported in Table 2.

Before surgery, all patients received a three-cycle chemotherapy regimen consisting of cisplatin–gemcitabine in 57 cases (72%; SL group: 30; PN group: 27), carboplatin–vinorelbine in 17 cases (22%; SL group: 7; PN group: 10), and cispaltin–paclitaxel in four cases (6%; SL group: 2; PN group: 2).

Patients have been classified according to the reviewed 7th edition of the tumor, node, metastasis clinical and pathological staging system for lung cancer.[15] The noninvasive staging assessment included total body computed tomography (CT) scan with contrast medium, fiberoptic bronchoscopy, and bone scintigraphy. Magnetic resonance of the brain was performed only in patients presenting contraindication for contrast medium at CT scan. Fludeoxyglucose positron emission tomography was performed before the oncological treatment only in those patients with suspected metastatic lesions found in CT scan since 2003.

The pulmonary functional assessment was performed by spirometry and blood gas analysis; additional functional tests such as stress tests and ventilation–perfusion lung scintigraphy were performed on patients at risk. Cardiac evaluation was routinely performed by electrocardiography; ecocardiography was performed for all patients with abnormal electrocardiography or previous history of cardiac disease.

All N2 diseases have been histologically or cytologically proven by mediastinoscopy or transbronchial needle aspiration before chemotherapy. The clinical IIIb stage group included only T4 N2 tumors.

The indication for induction chemotherapy in the stage IIb patients was because of the large size of the primary cancer associated with clinical evidence of hilar nodal involvement. A complete clinical restaging was performed after the induction treatment and before surgery by whole body CT scan with contrast medium and bronchoscopy. In addition, since 2004, all patients underwent fludeoxyglucose positron emission tomography scan before the operation. The surgical technique for sleeve resection and reconstruction of the bronchus and the PA has been previously reported.[16–18]

All the patients underwent operation 3 to 4 weeks after the end of induction therapy. We performed a bronchial SL in 21, a PA SL in 12, and a broncho-vascular SL in six patients, respectively. In one case, a right upper bronchial SL was

TABLE 2. Patients' Characteristics

Variable	SL Group ($n = 39$)	PN Group ($n = 39$)
Age (mean, yr ± DS, range)	63 ± 7.8 (47–78)	59.2 ± 10.37 (35–77)
Sex (male/female)	28/11	30/9
Smoke (*n*, %)	29 (74)	31 (79)
FEV 1[a] (% predicted ± DS)	88 ± 16	82 ± 21
Histology (*n*,%)		
Adenocarcinoma	23 (58.9)	11 (28.2)
Squamous	14 (35.9)	22 (56.4)
Mixed	1 (2.6)	3 (7.7)
Large-cell	1 (2.6)	3 (7.7)
Clinical stage before induction therapy (*n*, %)		
IIB	6 (15)	1 (3)
IIIa	30 (77)	36 (92)
IIIb	3 (8)	2 (5)

[a] After induction chemotherapy and before surgical resection.
SL, sleeve lobectomy; PN, pneumonectomy; FEV1, forced expiratory volume in 1 second.

associated with the superior vena cava resection and reconstruction by the interposition of a bovine pericardial conduit according to the previously described technique.[19] In all cases of sleeve resection, the bronchial anastomosis was protected by an intercostal muscle flap.

Pneumonectomy was on the right in 19 and on the left in 20 patients (in 7 cases it was intrapericardial and in 2 cases it was associated with en bloc resection of the chest wall). The bronchial stump was covered by a vascularized omental flap, harvested through the diaphragm in 16 patients considered at high risk for bronchial fistula occurrence. The technique and indication for the transdiaphragmatic transposition of the greater omentum have been previously reported.[20]

A systematic lymph node dissection was performed in all surgical procedures. Operative morbidity and mortality were considered within 30 days after surgery.

The oncological follow-up was performed by a total body CT scan repeated every 6 months for the first 2 years and once a year for the next 3 years. Fiberoptic bronchoscopy was performed after 1, 6, and 12 months from surgery, respectively and once a year for the next 4 years.

Comparison between Sleeve Lobectomy after Induction Therapy and Sleeve Lobectomy without Induction Therapy

In the study period (1998–2011), 138 patients (81 men and 57 women) underwent SL for NSCLC without induction therapy. Mean age of the patients was 65 ± 10.2 years (range, 45–81). Seventy-five percent of these patients were current smokers. The mean preoperative forced expiratory volume in 1 second (FEV1) was 84 ± 17% predicted. Sleeve resection was bronchial in 87, vascular in 29, and bronchovascular in 22 patients. All patients undergoing bronchovascular reconstruction presented with clinical stage Ib to IIIa-N1.

These patients were considered for comparison with those undergoing an SL after induction chemotherapy in the same period, to assess whether the preoperative treatment (chemotherapy) would affect postoperative outcome. Oncological results including long-term survival and recurrence rate were not compared because of the obvious significant differences existing between the two surgical groups (patients with or without induction therapy) in terms of tumor staging and type of nonsurgical treatment (neoadjuvant and adjuvant therapy).

Statistical Analysis

Data were collected and stored with an Excel database (Microsoft Corp, Redmond, WA). Quantitative variables were expressed as mean ± SD, whereas nominal variables were expressed binarily as presence (1) or absence (0) of the event. In the univariate analysis, qualitative variables were analyzed with the Pearson c^2 test or Fisher's exact test as required. Multivariate analysis was performed by Cox regression on variables that showed statistical significance at univariate analysis. Survival curves were plotted with the Kaplan–Meier formula; the log-rank test was performed to compare survival between different groups.

RESULTS

The mean FEV1 after induction therapy and before surgical treatment is reported in Table 2. There was no significant difference in terms of preoperative FEV1 between the two surgical groups ($p = 0.1$).

All patients underwent radical resection with free bronchial and vascular margins. Histological findings are reported in Table 2. Final pathological stage found in the SL group was: stage I in 17 (43.6%), stage II in 10 (25.6%), and stage III in eight (20.5%) patients. A complete pathological response was observed in four patients (10.3%) of this group. Pathological stage in the PN group was: stage I in six (15.4%), stage II in 15 (38.5%), and stage III in 18 (46.1%) patients. All patients classified as c-stage II in the SL group were downstaged as p-stage I after induction therapy. The other patients classified as pathological stage I or II, or as complete pathological response, presented a clinical stage III tumor before induction therapy. The downstaged patients rate (complete response, p-stage I–II) was 79.5% in the SL group and 53.8% in the PN group ($p = 0.01$).

Postoperative complications occurred in 13 cases in the PN group (33.3%) and in 11 patients undergoing SL (28.2%), without statistically significant differences between the two groups ($p = 0.6$). Complications after parenchymal sparing operations and PN are reported in Table 3. One patient, presenting late bronchial anastomotic stenosis in the SL group, was successfully treated by laser and stenting. The three patients experiencing postoperative bleeding in the PN group required rethoracotomy. No complications related to the vascular reconstruction occurred. One patient died postoperatively in the PN group as a result of sepsis after bronchopleural fistula (PN group postoperative mortality rate: 2.6%). No perioperative mortality was observed in the SL group. There was no significant difference in postoperative mortality between the two groups ($p = 0.3$).

TABLE 3. Postoperative Complications after Neoadjuvant Chemoterapy

Complication	SL (*n*)	PN (*n*)
Prolonged air leak	5	—
Atrial fibrillation	3	5
BPF–pleural empyema	—	2
Bleeding-retoracotomy	—	3
Atelectasis	1	1
Pneumonitis	1	—
Bronchial anastomotic stenosis	1	—
Pulmonary edema	—	1
Respiratory insufficency	—	1
Total	11	13

BPF, broncho-pleural fistula; SL, sleeve lobectomy; PN, pneumonectomy.

The median follow-up was 39 months (range, 2–139) (SL group: 37, range, 2–77; PN group: 36, range, 6–139). The recurrence rate was 20.5% (n = 8; locoregional 2, distant 6) in the SL group and 30.8% in the PN group (n = 12; locoregional 1, distant 11), but this difference was not statistically significant (p = 0.2). In particular, there was no significant difference between the two groups, if considering locoregional recurrence rate only.

Overall 3- and 5-year survival rates after SL were 68.3 ± 8% and 64.8 ± 8%, respectively. Overall 3- and 5-year survival rates after PN were 59.5 ± 5% and 34.5 ± 8%. The difference between the two groups in terms of overall 3-year survival was not statistically significant. The difference in terms of overall 5-year survival was statistically significant (p = 0.02), indicating a better prognosis for the SL group (Fig. 1). When considering 5-year survival rate according to pathological stages, a significant benefit was found after SL for patients with pathological stage I–II or complete response (the downstaged tumor patients) (SL group: 80 ± 8% versus PN group: 45 ± 7%, p = 0.04) (Fig. 2), whereas no significant difference between the two surgical options was reported for patients with pathological stage III (the not-downstaged tumor patients) (SL group: 25 ± 15% versus PN group: 27 ± 11%, p = 0.4). Disease-free (no recurrence) 3- and 5-year survival rates were 80 ± 6% and 73 ± 7%, respectively after SL, and 64.2 ± 7% and 59 ± 10%, respectively after PN (p = 0.1) (Fig. 3). Patients who died during the follow-up period because of a cause clearly related to the neoplastic disease were six in the SL group and 10 in the PN group (p = 0.4).

When considering the whole study population, a significant advantage in overall survival was found at univariate analysis for the following variables: SL versus PN, no recurrence versus recurrence, female versus male sex, preoperative FEV1 70% or more predicted versus less than 70% predicted, and tumor downstaging (complete response, p-stage I–II) versus no downstaging (p-stage III) (Table 4). At multivariate analysis, only the presence of recurrence, male sex, preoperative FEV1 less than 70% predicted, and pathological stage III were confirmed as negative prognostic factors (Table 5).

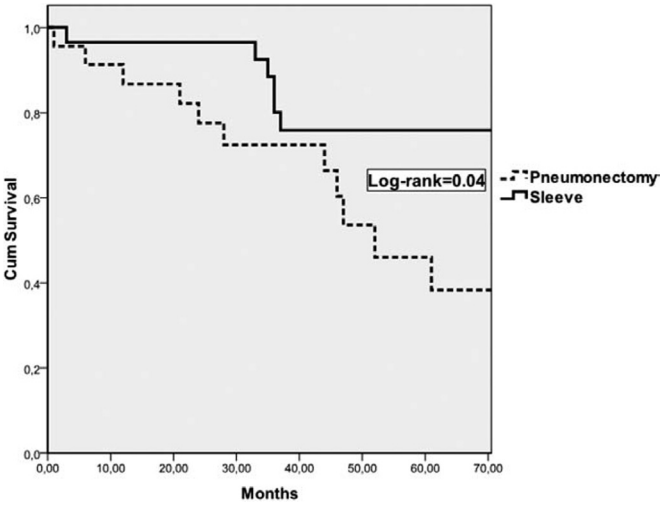

FIGURE 2. Survival curves of p-stage I–II (downstaged) patients after sleeve lobectomy or pneumonectomy.

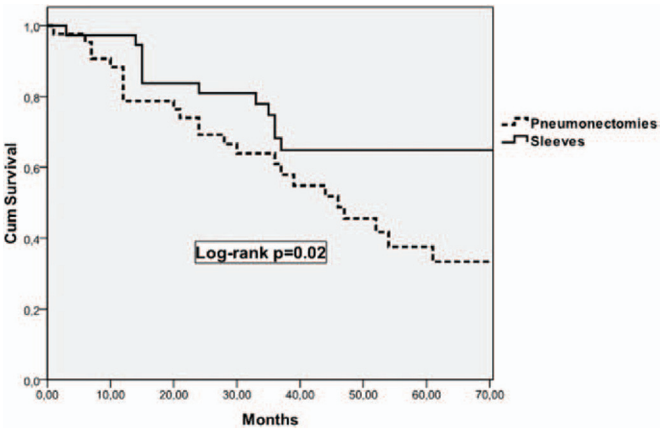

FIGURE 1. Survival curves of patients undergoing sleeve lobectomy or pneumonectomy after induction therapy.

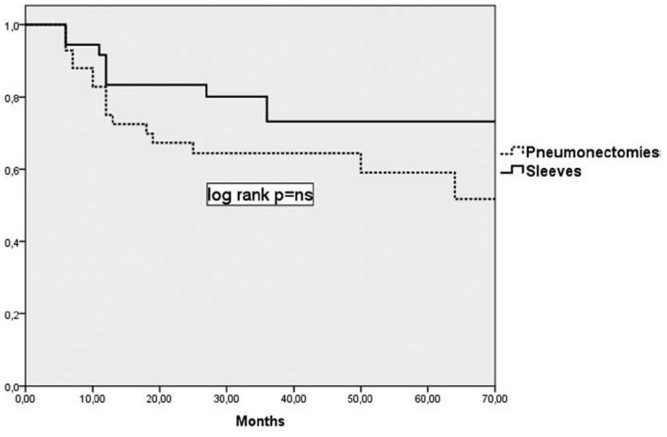

FIGURE 3. Disease-free survival curves of patients undergoing sleeve lobectomy or pneumonectomy after induction therapy.

TABLE 4. Factors Influencing Long-Term Survival, According to Univariate Analysis

Variable	±95%	*p*	OR
Surgery (PN/SL)	0.007	3.441	1.379–8.587
Side (R/L)	0.517	0.750	0.314–1.791
Recurrence (yes/no)	0.0001	20.956	5.484–80.081
Complications (yes/no)	0.446	1.448	0.558–3.759
Smoke (yes/no)	0.166	0.484	0.172–1.365
Heart disease (yes/no)	0.356	1.545	0.611–3.906
Age (yrs) (≥65/<65)	0.109	2.575	0.749–12.022
Sex (male/female)	0.001	8.077	2.150–30.339
FEV1 (%) (<70/≥70)	0.001	5.700	1.963–16.633
Histology (squamous/ nonsquamous)	0.727	1.169	0.486–2.812
Downstaging (no/yes)	0.002	4.321	1.637–11.405

L, left; OR, odds ratio; PN, pneumonectomy; R, right; SL, sleeve lobectomy; FEV1, forced expiratory volume in 1 second.

Comparison between Sleeve Lobectomy after Induction Therapy and Sleeve Lobectomy without Induction Therapy

All patients undergoing broncho-vascular reconstruction without induction chemotherapy received radical resection with free bronchial and vascular margins. Histology was adenocarcinoma in 74, squamous cell carcinoma in 57, large-cell carcinoma in five, and mixed in two patients, respectively. Postoperative complications occurred in 32 of these patients (23.2%). The most frequent complications were atrial fibrillation (9 patients), and parenchymal air leak (7 patients). Anastomotic stenosis after bronchial sleeve resection occurred in five patients who were successfully treated by laser (3 patients) or laser and stenting (2 patients). Other complications included pulmonary atelectasis (3 patients), wound suppuration (2 patients), pleural empyema (1 patient), pneumonitis (1 patient), chest wall hematoma (1 patient), phrenic nerve palsy (1 patient), and recurrent nerve palsy (1 patient). In one patient, a broncho-arterial fistula occurred at the anastomotic site, resulting in death. Overall postoperative mortality was 0.7% (1 of 138).

TABLE 5. Factors Influencing Long-Term Survival, According to Multivariate Analysis (Cox Regression)

			95.0% CI for Exp(B)	
Variables in the Equation	p	OR	Lower	Upper
Surgery (PN/SL)	0.481	0.719	0.287	1.801
Side (R/L)	0.240	1.562	0.742	3.288
Recurrence (yes/no)	0.007	0.359	0.172	0.751
Complications (yes/no)	0.912	0.952	0.395	2.292
Smoke (yes/no)	0.524	1.358	0.531	3.474
Heart disease (yes/no)	0.925	0.959	0.403	2.280
Age (yrs) (≥65/<65)	0.698	0.754	0.181	3.135
Sex (M/F)	0.027	0.232	0.064	0.848
FEV1 (%) (<70/≥70)	0.017	0.389	0.179	0.845
Histology (squamous/ nonsquamous)	0.125	0.489	0.196	1.218
Downstaging (no/yes)	0.044	0.442	0.200	0.977

CI, confidence interval; L, left; OR, odds ratio; PN, pneumonectomy; R, right; SL, sleeve lobectomy; FEV1, forced expiratory volume in 1 second.

The analysis of postoperative complication rates after SL did not show significant difference between patients undergoing broncho-vascular reconstruction without induction chemotherapy and patients receiving preoperative chemotherapy (23.2% versus 28.2%; $p = 0.5$). Similarly there was no significant difference in terms of postoperative mortality (0.7% versus 0%; $p = 0.5$).

There was no significant difference between patients undergoing direct surgery and patients treated with neoadjuvant chemotherapy in terms of postoperative intensive care unit admission rate (3.6% versus 5.1%; $p = 0.67$) and postoperative hospitalization (mean: 7.5 ± 86 days versus 7.8 ± 61 days; $p = 0.07$).

DISCUSSION

Sleeve resection for lung cancer is indicated for a tumor arising at the origin of a lobar bronchus or at the origin of the lobar branches of the PA, but not infiltrating far enough to require PN. In addition, a sleeve resection may be indicated when N1 nodes infiltrate the bronchus or the PA from the outside, and in such cases, a combined reconstruction of the bronchus and the PA may be required.

After induction therapy, reconstructive procedures may be indicated also when indissociable fibrotic tissue embed the PA and/or the bronchus. Oncologically, the primary goal in every case is complete resection of the tumor, with free resection margins.

Although broncho-vascular reconstructions associated with lobectomy represent surgical procedures with higher technical complexity when compared with standard major lung resections, postoperative morbidity and mortality data from a number of recent studies report overall better results for patients undergoing SL with respect to PN, especially when considering trials published after 2005, indicating the achievement of improved outcome with increased experience in reconstructive techniques (Table 1).

When analyzing survival data reported in literature over the last 20 years, most studies show similar or better results for parenchymal sparing resections when compared with PN. Moreover, in the analysis of 5-year survival according to stage and nodal status, SL results in higher survival rates for stages I and II, whereas the survival advantage in stage III seems to be limited (Table 1). These results justify the increasing use of parenchymal sparing procedures for lung cancer also in patients with good cardio-pulmonary function, as observed in the last years. Postoperative quality of life has been advocated as one of the strongest indicators that should influence the decision to perform an SL rather than a PN. A number of studies indicate that lung parenchyma sparing improves postoperative quality of life because of a greater pulmonary reserve. Gomez Caro[11] and Melloul[14] reported a statistically significant difference favoring SL in terms of postoperative loss of FEV1.

Induction chemotherapy represents a standardized indication for advanced-stage NSCLC patients because this treatment modality has been proven to allow improved local and systemic tumor control and survival benefit.[21,22] However, the administration of a neoadjuvant therapy has been frequently reported as a factor significantly increasing the risk for postoperative complications and mortality, although some recent prospective studies have demonstrated the possibility of performing major lung surgery safely even after induction treatment.[23]

The occurrence of complications can be related to technical reasons in the surgical management because of the anatomical alterations and tissue damage produced by the oncological treatment in the operative field. Moreover, the detrimental effect of chemotherapy on lung parenchyma, predisposing to acute respiratory distress syndrome and pneumonia, has to be considered.

In many experiences, the postoperative risk after induction therapy has been found to be significantly increased when a PN, especially on the right side, is performed.[24] The mortality rate after right PN after induction therapy has been reported between 14% and 43% in recent large series.[21,22,25] In the Southwest Oncology Group S9900 trial,[22] a 16.7% mortality rate has been reported in the PN group after induction chemotherapy in comparison with no mortality in the surgery-alone group. Worse results have been observed with the associated administration of preoperative irradiation. In a phase III trial by Albain et al.[21], analyzing the role of surgery after chemotherapy plus radiotherapy, a 26% operative mortality was registered after PN, leading to the conclusion that trimodality treatment may be beneficial if PN can be avoided.

Bronchial stump insufficiency with consequent broncho-pleural fistula and pleural empyema, and acute respiratory distress syndrome of the residual lung have been reported as the most frequent postpneumonectomy complications resulting in death, in main series analyzing risk factors for surgical morbidity and mortality after neoadjuvant therapy.

Very limited data are available in the literature when considering broncho-vascular reconstructions after induction therapy. Only few experiences have been published so far reporting the routine use of sleeve resection after neoadjuvant therapy.[23,26–30]

Although we along with other authors[23,26–28,30] have proved in the past years the possibility of performing even complex broncho-vascular reconstructive procedures after induction therapy with short-term and long-term results comparable with those of the standard procedures, special concern has been expressed by many thoracic surgeons when considering such operations because of the theoretically higher risk of perioperative complications and mortality. Scarring tissue and desmoplastic reaction produced by the neoadjuvant treatment generally increases the technical difficulty of bronchial and vascular hilar dissection and may be responsible for impaired bronchial healing, thus providing additional problems when performing a reconstructive procedure. It is interesting to note that in this study we have showed that patients undergoing SL after neoadjuvant chemotherapy report no significant difference in terms of postoperative morbidity and mortality when compared with those undergoing this operation without induction treatment.

To the best of our knowledge, no published large experience is actually available in the literature comparing short-term and long-term results of SL with those of PN after induction therapy. This study reports a trend toward lower morbidity and mortality rates in SL patients in comparison with PN patients receiving preoperative chemotherapy, although no significant difference was found.

Moreover, we have observed a significantly higher 5-year survival rate in patients undergoing broncho-vascular reconstruction with respect to those undergoing PN. This seems to be principally a result of the higher rate of patients showing response to therapy in the SL group (79% versus 53%) and also because at multivariate analysis, tumor downstaging has been found to be a significant factor influencing prognosis.

Moreover, a favorable impact on long-term survival because of the parenchymal sparing and consequent improved cardio-pulmonary status cannot be excluded. This positive effect on prognosis related to the better postoperative performance status is suggested by the lack of difference in disease-free survival rates between SL patients and PN patients found in this study. This indicates that the rate of patients surviving without recurrence is similar between the two groups, and therefore, better long-term prognosis observed after parenchymal sparing operations may not be justified only by oncological reasons. Furthermore, the number of patients who died during the follow-up period as a result of causes clearly related to neoplastic recurrence was lower in the SL group when compared with the PN group, although the difference was not significant.

When considering the theoretical increased bronchial healing complications incidence (bronchial stump insufficiency after a PN and anastomotic dehiscence after an SL) because of the effects of preoperative treatment on bronchial tissue, a significant reduction of this risk can be achieved by the systematic use of vascularized flaps.[20,24]

We routinely perform a protection (intercostals muscle flap) of the bronchial anastomotic line after an SL, and we consider this procedure as one of the key factors to the low anastomotic dehiscence rate observed in our experience even after induction therapy.

Similarly, over the last 15 years, we have standardized the use of viable tissue flaps, usually greater omentum, in patients undergoing PN after induction therapy considered at significantly increased risk for bronchial dehiscence, with the aim of reinforcing the bronchial stump.[20] This technical strategy has proved effective because no occurrence of broncho-pleural fistula has been observed in patients treated with this technique, and both the patients experiencing post-pneumonectomy broncho-pleural fistula in this series were operated in the early period of this study without the omental flap bronchial reinforcement because of technical or general contraindication for the omentoplasty procedure. The use of the greater omentum has been preferred to the muscular flap in PN patients as it provides a larger amount of tissue and a

rich vascular supply, assuring adequate oxygen and antibiotic delivery. Both these aspects may prove advantageous after PN, when an empty pleural cavity is present and the risk of empyema is higher. Moreover, the well-known immunologic action of the omentum may play a role in the prophylaxis of postpneumonectomy pleural infection.

A limitation of this study is represented by the nonhomogeneous induction therapy regimen administered, including different pharmacological options. However, because of the similar distribution of the different oncological therapeutic regimens between the two groups of patients (PN group and SL group), we think that this aspect is unlikely to influence the results. Another issue to be considered is related to the criteria used for the decision to perform an SL or a PN. These are principally based on tumor extent and intraoperative surgeon's judgment, and therefore, could represent a theoretical bias. Patients with larger tumors are more likely to receive a PN. This aspect may justify the higher rate of downstaged tumors among patients undergoing broncho-vascular reconstruction. Moreover, we have observed a higher rate of squamous cell carcinoma in the PN patients; this finding may have influenced the response to the induction chemotherapy in this group.

In conclusion, SL represents a valid therapeutic option even after induction chemotherapy, providing better long-term survival than PN, with no increase of postoperative complications and recurrence rate. Pathological downstaging is a favorable prognostic factor.

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